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Depression and Dementia: The Role of Cortisol and Vascular Brain Lesions. AGES-Reykjavik Study

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Abstract.
Background: Late-life depression (LLD) is related to an increased risk of developing dementia; however, the biological mechanisms explaining this relationship remain unclear.
Objective: To determine whether the relationship between LLD and dementia can be best explained by the glucocorticoid cascade or vascular hypothesis.
Methods: Data are from 4,354 persons (mean age 76 ± 5 years) without dementia at baseline from the AGES-Reykjavik Study. LLD was assessed with the MINI diagnostic interview (current and remitted major depressive disorder [MDD]) and the Geriatric Depression Scale-15. Morning and evening salivary cortisol were collected (glucocorticoid cascade hypothesis). White matter hyperintensities (WMH; vascular hypothesis) volume was assessed using 1.5T brain MRI. Using Cox proportional hazard models, we estimated the associations of LLD, cortisol levels, and WMH volume with incident all-cause dementia, AD, and non-AD dementia.
Results: During 8.8 ± 3.2 years of follow-up, 843 persons developed dementia, including 397 with AD. Current MDD was associated with an increased risk of developing all-cause dementia (HR = 2.17; 95% CI 1.66–2.67), with risks similar for AD and non-AD, while remitted MDD was not (HR = 1.02; 95% CI 0.55–1.49). Depressive symptoms were also associated with increased risk of dementia, in particular non-AD dementias. Higher levels of evening cortisol increased risk of dementia, but this was independent of MDD. WMH partially explained the relation between current MDD and dementia risk but remained increased (HR = 1.71; 95% CI 1.34–2.08).
Conclusion: The current study highlights the importance of LLD in developing dementia. However, neither the glucocorticoid cascade nor the vascular hypotheses fully explained the relation between depression and dementia.

Keywords: Cerebrovascular disorders, cohort studies, dementia, depression

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INTRODUCTION

Prospective studies have shown that late-life depression (LLD) increases the risk of dementia, including Alzheimer's disease (AD) and vascular

dementia [1–3]. Notably, a recent review demonstrated that depression shows the most consistent evidence as a risk factor for dementia [4]. However, little is known about the neurobiological mechanisms underlying the relation between LLD and dementia and to what extent LLD is a risk factor or a prodromal stage of dementia [2]. There are two main hypotheses for this connection: the glucocorticoid cascade hypothesis [5], which stipulates that depression [6] leads to AD through age-associated hippocampal atrophy and increased levels of cortisol due to dysregulation of the hypothalamic-pituitary-adrenal axis [1, 7–13]; and the vascular hypothesis, stating that depression precedes dementia through small vessel changes in mood-regulating areas resulting from or contributing to depression [2, 14–16]. One study showed that cerebrovascular disease explained cognitive deficits in LLD better than salivary cortisol levels [17], but there is a lack of longitudinal studies that jointly investigate these hypotheses with dementia [18]. This is important, as better understanding of the role of depression in the etiology of dementia, may help develop strategies to prevent, delay, or treat the disease.

We aimed to investigate the relationships between LLD, cortisol levels, white matter hyperintensity (WMH) volume and incident dementia in a large community-based prospective cohort study of older persons. We hypothesized that LLD increased the risk of dementia [4]; that higher evening cortisol levels interact with LLD to increase dementia risk, particularly AD, reflecting the glucocorticoid cascade; and that larger WMH volume partially explained the relationship between current LLD and dementia, reflecting the underlying contributing factor of WMH in both LLD and dementia.

METHODS

Study population

The Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study is a population-based prospective cohort study of the National Institute on Aging and the Icelandic Heart Association, initiated to investigate the genetic and environmental factors contributing to clinical and subclinical disease at older age [19]. It is a continuation of the Reykjavik Study, which was initiated in 1967 by the Icelandic Heart Association, and included men and women born in 1907 to 1935 and living in the Reykjavik area [19]. The original cohort of the Reykjavik Study was examined 1 to 6 times according to a schedule that allowed longitudinal and cross-sectional analyses over the 30-year follow-up period. From 2002 through 2006, 5,764 individuals (mean age: 76 years) randomly chosen from the survivors of the Reykjavik Study were examined for the AGES-Reykjavik Study. They underwent comprehensive assessments at the Reykjavik research center including comprehensive questionnaires, blood tests, biometry, 1.5 Tesla brain MRI, and depression, cognitive, and dementia assessments.

From 2007 to 2011, 3,316 persons received one follow-up examination. Monitoring of incident dementia diagnoses continued until a maximum of 12 years follow-up time. Reasons for loss to follow-up have been described elsewhere [20].

Standard protocol approvals, registrations, and patient consents

The AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Icelandic Data Protection Authority, and by the Institutional Review Board for the National Institute on Aging, NIH. Written informed consent was obtained from all participants.

Dementia diagnosis

The procedure for dementia assessment at baseline and follow-up has been described elsewhere [20–22]. In brief, dementia ascertainment and classification of subtypes was performed using a 3-step protocol following international criteria. A cognitive screening of the total sample was performed, with a detailed neuropsychological exam in screen positives and a further neurologic and proxy exam performed in step 2 persons who screened positive on test results. A consensus diagnosis according to international guidelines was made by a multidisciplinary panel including a neurologist, geriatrician, neuroradiologist, and neuropsychologist. Additional cases were identified through medical and nursing home records, as well as death certificates. When an individual moved into a nursing home, all-cause dementia and AD diagnosis was based on the intake exam into the nursing home. Additional cases were identified in the nursing home following a standardized protocol followed by all Icelandic nursing homes [23]. For the present study, we defined all-cause dementia, AD dementia, and other dementias.

Depression assessment

Depression measures have been described in detail elsewhere [24]. Briefly, remitted and current (i.e., in the past two weeks) diagnosis of major depressive disorder (MDD) was assessed with the Mini-International Psychiatric Interview (MINI) diagnostic interview [25] by trained health professionals at baseline. For the purpose of this study, we categorized participants into three groups: never MDD, remitted (past) MDD, and current MDD.

The Geriatric Depression Scale-15 (GDS-15) [26] was administered and categorized using the cutoff of 6 or higher to indicate elevated depressive symptoms.

Cortisol measures

Measures of cortisol have been described in more detail elsewhere [13]. Using Salivette® devices (Sarstedt, Rommelsdorf, Germany), saliva samples were collected at night the day before visiting the clinic and the next morning 45 min after awaking. Instructions were given not to eat, drink, or brush teeth before sampling. Salivary cortisol was analyzed with a time-resolved immunoassay with fluorescence detection (Delfia; PerkinElmer, Waltham, MA) [27]. Inter-assay variability was below 12% and intra-assay variability was below 10%. The lower detection limit was 0.43 nmol/L. We excluded 0.7% of the morning samples and 0.5% of the evening samples as they had values of > 100 nmol/L which were considered unreliable. Morning and evening levels of cortisol were natural log-transformed due to skewed distribution and z-scores were calculated.

Brain MRI and brain segmentation

The MRI protocol and segmentation procedure have been described elsewhere [13, 28]. In short, eligible participants underwent MRI on a 1.5T Signa Twinspeed system (General Electric Medical Systems, Waukesha, WI) including a 3-dimensional axial T1-weighted spoiled gradient echo sequence, a fluid attenuated inversion recovery (FLAIR) sequence, a proton density/T2-weighted (PD/T2) fast spin echo sequence, and a T2*-weighted gradient echo type echoplanar sequence. The FLAIR, PD/T2 and T2* sequences were acquired with 3 mm thick interleaved slices. Regional gray and white matter, cerebrospinal fluid (CSF), and WMH were segmented automatically with an AGES-Reykjavik Study modified algorithm described elsewhere [28]. In brief, an artificial neural network classifier categorized each voxel as belonging to either gray matter, white matter, CSF, or WMH. The automatic classification was further validated by having a trained radiographer assess a sample of MRI scans [28]. Visible hyperintense lesions on both T2-weighted and FLAIR images were classified as WMHs [29]. WMHs were classified by trained radiographers using the Achten Scale, which takes into account both lesion size and number [30].

Covariates

Covariates assessed with questionnaires included age, sex, educational level (categorized into three categories [primary, secondary, college/university] from four categories [primary, secondary, college, university]), smoking history (current versus non-smoker), alcohol intake (gram/week), and physical activity (never, rarely, occasionally, moderate, or high in the past 12 months). Body mass index (BMI) was calculated from height and weight and expressed as kg/m^2. Systolic and diastolic blood pressure was measured with a standard mercury sphygmomanometer. Hypertension was defined as systolic blood pressure of $\geq$ 140 mm Hg or diastolic blood pressure of $\geq$ 90 mm Hg, use of antihypertensives or self-reported physician's diagnosis of hypertension. Diabetes mellitus was defined as use of blood glucose-lowering drugs or fasting blood glucose level $\geq$ 7.0 mmol/L or self-reported history of diabetes. *APOE* genotyping was carried out using the microplate array diagonal gel electrophoresis (MADGE) system [31].

Analytical sample

Of the 5,764 members of the cohort, a total of 4,349 had no dementia and brain MRI segmentation available. The majority of people not having a MRI had a home visit, scheduling conflicts, contraindications, or refused. A small proportion of those with MRI did not have brain segmentation (missing sequences or movement artefacts [20, 24, 29]). The average age of those who had an MRI was 76 years compared to 80 years in those who did not receive an MRI. Of those who received a MRI, 58% were women compared to 55% in those who did not receive an MRI. Average score on the GDS-15 was 2 in those who received an MRI and 3 in those who did not. Of those with a brain MRI, 4% had ever MDD diagnosis compared to 3% in those without brain MRI. Average morning cortisol levels were 19.8 nmol/L in those who had a

brain MRI compared to 17.8 nmol/L in those who did not. Evening cortisol in those with a brain MRI was 3.9 nmol/L and 4.4 nmol/L in those without.

Data analysis

Participants were followed from date of inclusion until diagnosis of dementia, death, loss to follow-up, or end of follow-up (October 2015), whichever came first. Censoring date for participants who received a diagnosis of dementia during follow-up was set halfway between date of inclusion and follow-up visit. For incident cases identified through nursing homes, date of diagnosis was based on the nursing home intake exam or the date when the nursing home staff diagnosed dementia based on a standardized protocol followed by all Icelandic nursing homes. For those who died, the censoring date was date of death. Those lost to follow-up were assumed not to have dementia, and the censoring date was set halfway between date of inclusion and end of follow-up. Multiple imputation (AregImpute in R version 2.13.1) was used to address missing values at baseline (0–9.3% [medication use]). Incident dementia was not used for imputation. R (epiR, survival, and survminer in version 3.6.1) was used for the data analyses. Pooled results of 10 datasets are presented. Proportional hazards assumption (i.e., Schoenfeld's residuals), influential observations (i.e., dfbetas), and nonlinearity (i.e., martingale residuals) were checked. Cox regression models used age as the timescale. Sex and level of education were added as covariates. Lastly, stratified results by sex are additionally presented to explore possible sex differences.

Depression and risk for dementia

We calculated baseline characteristics for the total study sample and according to depression diagnosis (no history of MDD, remitted MDD, and current MDD). Cox proportional hazard models were fit to estimate the hazard ratio (HR) of the associations of lifetime MDD, current and remitted MDD compared with never MDD with incident all-cause dementia, AD, and other (non-AD) dementias. To further assess the aspect of time from baseline depression to dementia diagnosis, we fit models stratified by time from depression assessment at baseline to dementia diagnosis with a cut-off of 7 years follow-up time. Models were fit using depressive symptoms (i.e., the GDS-15) because dementia cases were too few when analyzing current MDD.

Glucocorticoid cascade hypothesis

To investigate the role of glucocorticoids, the relationship between morning and evening cortisol (i.e., the z-score of natural log-transformed values) with incident dementia was estimated. Next, morning and evening cortisol levels were added to the model with depressive symptoms. To estimate additive interaction [32] and the relative excess risk due to interaction, four groups with or without depression (defined by GDS-15 scores <6 or 6 or higher, as there were too few cases with current MDD) and low/normal or high levels of evening cortisol (defined as the highest tertile of evening cortisol >3.3 nmol/L versus the lower two tertiles) were created and their relationship with later dementia outcome was explored. Dummy variables were used for ease of interpretation of the interaction [33] with confidence intervals from Hosmer and Lemeshow [34]. We additionally estimated additive interaction using continuous measurements [32], standardizing with z-scores both GDS-15 scores and log-transformed cortisol levels.

Vascular hypothesis

Similarly, depressive symptoms and total WMH volume (i.e., the z-score of natural log-transformed values) were entered together into the Cox regression model to explore the vascular hypothesis, with standardized intracranial volume (ICV) added as a covariate. Next, the relative excess risk due to interaction of high depressive symptoms and larger WMH volumes on dementia risk was estimated by calculating four dummy variables where large WMH volume was defined as the highest tertile of ICV-corrected natural log-transformed WMH volume (>0.28% ICV) and GDS-15 scores of 6 or higher were used to indicate presence of depression. We also assessed additive interaction using continuous measurements, of standardized GDS-15 score and log-transformed WMH volume.

Glucocorticoid cascade and vascular hypotheses

Additionally, to explore to what extent the glucocorticoid cascade and vascular pathways are independent contributors, cortisol levels and WMH volume were entered together in a model with depression diagnosis. To correct for vascular risk factors, additional adjustments were made for *APOE* genotype ($\varepsilon 4$ positive versus $\varepsilon 4$ negative), current smoking (versus never or former), alcohol intake (gram/week), physical activity (never, rarely, occasionally, moderate, or high in the past 12 months),

Table 1
Baseline characteristics of study sample ($N = 4,349$) according to depression diagnosis.

	Never MDD $n = 4155$	Past MDD $n = 130$	Current MDD $n = 64$	Total $N = 4,349$
Age, mean (SD), y	76 (5)	74 (5)	75 (5)	76 (5)
Women, no. (%)	2,417 (58)	88 (68)	42 (66)	2,547 (59)
Primary education, no. (%)	1,373 (33)	43 (33)	20 (31)	1,435 (33)
Current smoker, no. (%)	490 (12)	21 (16)	12 (19)	523 (12)
Alcohol use, mean (SD), gr/week	15 (33)	9 (19)	19 (49)	15 (33)
Physical activity, moderate/high, no. (%)	1,352 (33)	41 (32)	10 (16)	1,403 (32)
Body mass index, mean (SD)	27 (4)	28 (4)	28 (5)	27 (4)
Blood pressure, systolic, mean (SD), mmHg	142 (20)	138 (18)	138 (20)	142 (20)
Blood pressure, diastolic, mean (SD), mmHg	74 (10)	74 (10)	74 (9)	74 (10)
Hypertension, no. (%)	3,342 (80)	100 (77)	47 (73)	3,489 (80)
Diabetes, no. (%)	451 (11)	21 (16)	12 (19)	484 (11)
APOE ε4 positive, no. (%)	1,131 (27)	33 (25)	21 (33)	1,185 (27)
History of MDD, no. (%)	0 (0)	130 (100)	48 (75)	194 (4)
GDS-15, 6+, no. (%)	221 (5)	25 (19)	39 (61)	285 (7)
Morning cortisol, median (IQR), nmol/L	17.3 (15.7)	14.1 (15.9)	15.0 (19.0)	17.3 (15.8)
Evening cortisol, median (IQR), nmol/L	2.3 (2.4)	2.0 (2.6)	2.5 (4.0)	2.3 (2.4)
WMH, median (IQR), ml	13.5 (18.1)	11.6 (16.3)	14.6 (20.2)	13.5 (18.1)

MDD, major depressive disorder; GDS-15, Geriatric Depression Scale-15; WMH, white matter hyperintensities.

Table 2
Hazard ratios (HR) for the relation between late-life depression and risk of dementia ($N = 4,349$)

	All-cause dementia		Alzheimer's disease		Other dementias	
	No. of cases	($n = 843$) HR (95% CI)	No. of cases	($n = 397$) HR (95% CI)	No. of cases	($n = 446$) HR (95% CI)
Never MDD ($n = 4,155$)	808	1 (reference)	379	1 (reference)	429	1 (reference)
Ever MDD ($n = 194$)	35	1.37 (1.03–1.72)	18	1.38 (0.91–1.86)	17	1.43 (0.94–1.92)
Never MDD ($n = 4,155$)	808	1 (reference)	379	1 (reference)	429	1 (reference)
Remitted MDD ($n = 130$)	18	1.02 (0.55–1.49)	9	0.98 (0.31–1.65)	9	1.06 (0.40–1.72)
Current MDD (including past) ($n = 64$)	17	2.17 (1.66–2.67)	9	2.32 (1.63–3.02)	8	2.35 (1.61–3.09)
GDS-15 score < 6 ($n = 4,078$)	777	1 (reference)	370	1 (reference)	408	1 (reference)
GDS-15 score 6 or higher ($n = 271$)	66	1.31 (1.05–1.57)	27	1.16 (0.77–1.55)	38	1.49 (1.14–1.85)

Models are adjusted for age (timescale), sex, and level of education. MDD, major depressive disorder; GDS-15, Geriatric Depression Scale-15.

BMI, hypertension, and diabetes mellitus. ICV was also added as a covariate in the model.

RESULTS

Of the 4,349 participants without dementia at baseline, the mean age was 76 ± 5 years and 59% were women; 194 had a lifetime diagnosis of MDD, 130 of whom had a past diagnosis, and 64 a current diagnosis of MDD (Table 1). Of those with a current diagnosis, 75% also had a history of MDD. Median (10–90%) morning cortisol level in the study sample was 17.3 (5.6–36.2) nmol/L, and median evening cortisol level 2.3 (0.9–6.9) nmol/L. During a total of 38,221 person-years of follow-up (mean per person 8.8 ± 3.2 years, range 0.11–13.4 years), 843 persons developed dementia, 397 of whom had a diagnosis AD, and 446 were diagnosed with dementias other than AD.

Depression and risk for dementia

Of the 843 persons with incident dementia, 35 had a lifetime diagnosis of MDD. Cox regression analysis adjusted for age (timescale), sex, and education showed that the risk of dementia for lifetime MDD was increased (HR 1.37; 95% CI 1.03–1.72). Current MDD increased the risk of dementia more than twofold (HR 2.17; 95% CI 1.66–2.67), whereas remitted MDD was not associated with incident dementia (HR 1.02; 95% CI 0.55–1.49). Similar risks were observed for AD and non-AD dementias, although 95% confidence intervals were wider (Table 2). Depressive symptoms were also associated with increased risk of dementia, in particular non-AD dementias (Table 2).

Table 3
Hazard ratios (HR) for the relation between baseline depressive symptoms and risk of dementia, stratified for follow-up time ($N = 4,349$)

	All-cause dementia		Alzheimer's disease		Other dementias	
	No. of cases	($n = 843$) HR (95% CI)	No. of cases	($n = 397$) HR (95% CI)	No. of cases	($n = 446$) HR (95% CI)
Less than 7 years between baseline depression and time of dementia diagnosis ($N = 1330$)						
GDS-15 score < 6 ($n = 1,213$)	367	1 (reference)	191	1 (reference)	176	1 (reference)
GDS-15 score 6 or higher ($n = 117$)	42	1.30 (0.97–1.63)	17	1.00 (0.49–1.52)	25	1.77 (1.33–2.21)
7 years or more between baseline depression and time of dementia diagnosis ($N = 3019$)						
GDS-15 score < 6 ($n = 2,851$)	410	1 (reference)	178	1 (reference)	232	1 (reference)
GDS-15 score 6 or higher ($n = 168$)	24	0.97 (0.56–1.39)	11	1.01 (0.40–1.62)	13	0.96 (0.38–1.53)

Models are adjusted for age (as timescale), sex, and level of education. GDS-15, Geriatric Depression Scale-15.

To assess time between depression assessment and dementia onset, those who had a less than 7-year gap between baseline depressive symptoms and dementia diagnosis had a greater risk of developing dementia during that time, although the estimate did not reach statistical significance (HR 1.30; 95% CI 0.97–1.63), whereas no association was observed between high depressive symptomology and dementia in those who had a 7-year or greater interval (HR 0.97; 95% CI 0.56–1.39) (Table 3). Number of incident dementia cases in those with current MDD were too small to stratify by time interval. Results were similar for both men and women, except for depressive symptoms, which showed an increased risk for all-cause dementia only in men (Supplementary Table 1).

Glucocorticoid cascade hypothesis

When depression diagnosis and cortisol levels were entered together in the Cox regression analyses, the risk of all-cause dementia for current MDD remained increased (HR 2.09; 95% CI 1.59–2.59) (Fig. 1, model 2a). Similar patterns in associations were seen for AD and non-AD dementias. The relative excess risk due to interaction to calculate additive interaction [32] did not suggest interaction (Table 5, Supplementary Table 3). Since we found no association between morning cortisol and dementia, we did not further examine the interaction of depressive symptoms and morning cortisol levels on dementia.

When analyzed for men and women separately, the increased risk of current MDD with all-cause dementia and dementias other than AD was stronger in men, while evening cortisol was slightly stronger associated with all types of dementia in women and lost statistical significance in men (Supplementary Table 2).

Vascular hypothesis

When WMH volume was added to the model (Fig. 1, model 2b), the association of current MDD and incident all-cause dementia (HR 2.00; 95% CI 1.50–2.49), AD, and non-AD dementia attenuated; however, it remained statistically significant. Table 5 shows the joint association of high levels of depressive symptoms with large WMH volume on dementia risk. HRs were strongest for the combination of depressive symptoms and large WMH volume, although the relative excess risk due to interaction to calculate additive interaction [32] did not suggest interaction. Results were similar for men and women (Supplementary Table 2).

Glucocorticoid cascade and vascular hypotheses

When cortisol levels and WMH volume were entered together in a model with depression diagnosis, higher evening cortisol, and higher WMH volume were each independently associated with increased risk of dementia (Fig. 1, model 3a; Table 4). After adjusting for *APOE* genotype, current smoking, alcohol intake, physical activity, BMI, hypertension, and diabetes mellitus (Fig. 1, model 3b), associations attenuated further, but remained statistically significant. When all analyses were repeated with GDS-15 score, the association with incident dementia was weaker (HR 1.09; 95% CI 1.06–1.12), yet increased. HRs barely changed after further adjustment for cortisol levels, WMH volume, and other covariates (Fig. 1).

Due to using age as timescale, proportional hazards for sex were not met due to differences in risk for dementia between men and women in age in the models for AD. As noted in Supplementary Figure 1, risk for dementia was higher for women than men dur-

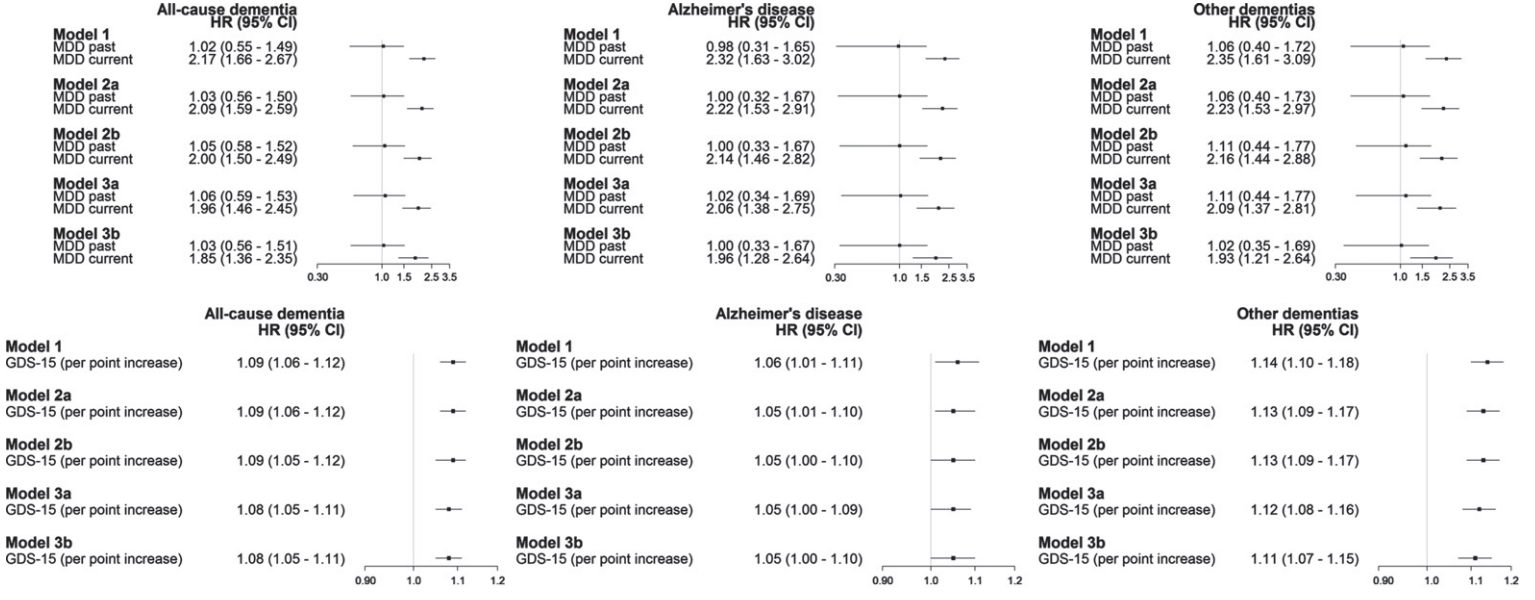

Fig. 1. Hazard ratios for the association of depression with dementia. model 1: adjusted for sex and education. model 2a: model 1 + morning cortisol and evening cortisol. model 2b: model 1 + white matter hyperintensity volume (WMH) and intracranial volume (ICV). model 3a: model 1 + morning cortisol, evening cortisol, WMH, and ICV. model 3b: model 3a + current smoking, alcohol intake, physical activity, body mass index, hypertension, diabetes mellitus, and *APOE* ε4 allele.

Table 4
Hazard Ratios (HR) of the independent and combined association of MDD, cortisol levels and WMH volume with incident dementia

	All-cause dementia ($n = 843$) HR (95% CI)	Alzheimer's disease ($n = 397$) HR (95% CI)	Other dementias ($n = 446$) HR (95% CI)
Remitted MDD	1.06 (0.59–1.53)	1.02 (0.34–1.69)	1.11 (0.44–1.77)
Current MDD (including past)	1.96 (1.46–2.45)	2.06 (1.38–2.75)	2.09 (1.37–2.81)
Morning cortisol	0.99 (0.92–1.07)	1.03 (0.92–1.14)	0.97 (0.87–1.07)
Evening cortisol	1.13 (1.06–1.20)	1.16 (1.06–1.26)	1.15 (1.04–1.25)
WMH volume	1.30 (1.22–1.37)	1.25 (1.15–1.36)	1.43 (1.33–1.53)

Adjusted for sex, education, and intracranial volume. WMH, white matter hyperintensities; MDD, major depressive disorder. Cortisol levels and WMH volume per SD increase.

Table 5
Hazard ratios (HR) for the independent and combined association of depressive symptoms, evening cortisol, and white matter hyperintensities volume with incident dementia

	All-cause dementia ($n = 843$) HR (95% CI)	Alzheimer's disease ($n = 397$) HR (95% CI)	Other dementias ($n = 446$) HR (95% CI)
Neither ($n = 2{,}804$)	1	1	1
Depressive symptoms ($n = 165$)	1.37 (1.02–1.72)	1.13 (0.58–1.68)	1.66 (1.19–2.12)
High evening cortisol ($n = 1{,}261$)	1.29 (1.14–1.44)	1.30 (1.08–1.52)	1.41 (1.20–1.62)
Both ($n = 120$)	1.51 (1.11–1.91)	1.44 (0.88–2.00)	1.74 (1.14–2.34)
Additive RERI (95% CI) [32]	**–0.15 (–1.74–1.44)**	**0.01 (–2.49–2.50)**	**–0.33 (–2.66–2.00)**
Neither ($n = 2{,}732$)	1	1	1
Depressive symptoms ($n = 168$)	1.43 (1.07–1.80)	1.40 (0.90–1.90)	1.54 (1.01–2.07)
Larger WMH ($n = 1{,}333$)	1.51 (1.37–1.65)	1.35 (1.14–1.56)	1.83 (1.63–2.02)
Both ($n = 117$)	1.71 (1.34–2.08)	1.16 (0.52–1.80)	2.47 (1.99–2.95)
Additive RERI (95% CI) [32]	**–0.23 (–1.85–1.38)**	**–0.59 (–2.25–1.08)**	**0.10 (–3.28–3.48)**

Adjusted for sex and education. RERI, relative excess risk due to interaction; WMH, white matter hyperintensities. The additive RERI is calculated with the epi.interaction() function in the epiR package in RStudio with Hosmer and Lemeshow confidence intervals. The equation for calculating the additive RERI is $(HR_{A+B+} - 1) - (HR_{A+B-} - 1) - (HR_{A-B+} - 1)$ [32]. Therefore, RERI = (1.51 – 1) – (1.37 – 1) – (1.29 – 1) = –0.15.

ing older age, which has also been seen previously in population-based cohorts [35].

DISCUSSION

The aim of our study was to investigate two leading hypotheses explaining the relation between LLD and risk of dementia. We found that a lifetime diagnosis of MDD increased the risk of dementia 1.4 fold, and that a current—not remitted—diagnosis of MDD in older persons without dementia was associated with a two-fold risk for incident dementia over 13 years follow-up, including AD and non-AD dementia, confirming estimates found in meta-analyses [3, 36]. Similarly, more depressive symptoms were also associated with increased risk of dementia, particularly non-AD dementia.

One of the prevailing hypotheses to explain the increased risk of dementia with depression has been the glucocorticoid cascade hypothesis [5]. In our study, we observed that higher evening, but not morning, cortisol increased the risk of developing dementia, including AD and non-AD dementia, but cortisol was an independent contributor and did not explain the relation between LLD and dementia. Thus, we found no evidence to support this hypothesis. Increased cortisol levels have been previously found in patients with dementia [37] and have been shown to predict dementia [38]. However, results are inconclusive regarding the timing of cortisol measure, as morning, evening, and diurnal variation in cortisol have been shown to predict dementia onset [39, 40]. In our study, we found a relation with evening cortisol only, which is consistent with a previous study where we showed that evening cortisol more so than morning cortisol was related with lower brain volumes [13]. Other studies also found that evening cortisol levels are associated with increased age [41], hypertension [42], diabetes [43], and neurodegeneration [13, 44].

Another proposed hypothesis linking LLD with dementia is the vascular depression hypothesis [2, 14–16], as vascular brain pathology has often been associated with LLD [45]. In another cohort, we pre-

viously showed that lacunar infarcts are related to higher and more fluctuating depressive symptoms at follow-up [46], as well as in those with cerebrovascular disease [47]. Our current results confirmed other studies that more WMH increased the risk of dementia [47, 48], but it only partially explained the relationship between MDD and dementia. Also, while the additive association of high depressive symptoms and more WMH was strongest for non-AD dementias, it did not suggest moderation or mediation.

While other studies have looked at either dementia or depression with WMH or cortisol, studies exploring the simultaneous influence of glucocorticoid and vascular pathways on depression and dementia are scarce. Comparable findings were reported in a small preceding study with 18 months of follow-up where stronger evidence was found for a mediating role of cerebrovascular lesions than for cortisol levels in the relation between depression and dementia in older depressed persons [17]

The association between current depression and dementia prevailed after correcting for additional cardiovascular risk factors, with WMH having a greater relationship with risk than evening cortisol. This is in line with a recent study that found WMHs were independently associated with cognitive decline and GDS-15 scores [49] and highlights the role of cerebrovascular disease in dementia and depression [50].

Our findings of that current but not past depression increased dementia risk could be interpreted as LLD being a prodromal stage of dementia. Indeed, a study with 28 years of follow-up [48] found that depressive symptoms increased prior to dementia diagnosis, suggesting that depression increases dementia risk closer to the time of dementia diagnosis. Consistent with this, in our study, those with a shorter time period between depression assessment and dementia diagnosis had a higher risk of developing dementia, particularly dementia other than AD, whereas those with a longer time period between depression and dementia diagnoses were not at higher risk. It should be noted that we were only able to stratify the sample for depressive symptoms (i.e., GDS-15 score) and not current MDD because of small numbers, and we therefore do not know who had previous episodes of depressive symptoms. Indeed, in our sample of participants with current MDD, the vast majority also had a history of MDD, and the association may partly reflect previous episodes of depression. Potentially, different mechanisms underlie different subtypes of LLD depending on history of MDD, age of onset, and number of previous episodes. To further unravel the direction of causation, similar studies with multiple measures of depression and longer follow-up are needed.

Strengths include the community-based population, the prospective design with long follow-up, the large sample size, and the complete ascertainment of incident dementia. Further, LLD was assessed with a structured diagnostic interview in addition to a depressive symptom questionnaire.

A limitation of this study is that current MDD was assessed with a two-week time window rather than 6 or 12 months. Therefore, the number of participants with current MDD was low and risk estimates had wide confidence intervals. We could not examine the combined association of current MDD and high cortisol or WMH volume and instead relied on depressive symptoms (although, results were similar for high WMH volume with current MDD compared to using depressive symptoms). Further, it is preferred to include samples of cortisol collected over multiple days [13, 51], to decrease possible within-participant variability [52, 53]; however, due to the large sample size of our cohort, we were only able to include one-day measurements. By investigating cortisol in such a large sample, the large variation on group level may have reduced the possibility of intra-subject variation.

The current study highlights the importance of LLD in developing dementia. While higher basal cortisol levels and WMH were also associated with increased risk of dementia, they were not a major mechanism underlying the relation between depression and risk of dementia. Future studies with long follow-up and repeated measures of LLD should investigate other explanatory factors and subtypes of LLD to further elucidate the pathophysiology behind depression and dementia and investigate to what extent LLD is a susceptibility feature of dementia rather than a causal risk factor.

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SUPPLEMENTARY MATERIAL

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